Docket No.: 649218007US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Michael D. Laufer

Application No.: 09/095,323 Confirmation No.: 9521

Filed: June 10, 1998 Art Unit: 3769

For: METHOD AND APPARATUS FOR TREATING SMOOTH MUSCLES IN THE WALLS OF BODY CONDUITS Examiner: D. M. Shay

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

As required under § 41.37(a), this brief is filed more than two months after the Notice of Appeal filed in this case on May 13, 2009, and is in furtherance of said Notice of Appeal.

As a preliminary matter, the examination of this application has been inconsistent during the more than eleven years that the application has been pending. As background, Examiner Shay rejected earlier claims over Clarke in a Final Office Action dated 19 July 2001, and the Appellants filed an Appeal Brief dated 25 January 2002 appealing the rejection over Clarke. After staying the prosecution for 3.5 years, the Board of Patent Appeals and Interferences issued an Order Returning Undocketed Appeal to the Examiner dated 2 September 2005 because Examiner Shay provided a new ground of rejection in the Answer based upon a combination of Clarke with

Waksman. The claims were formally rejected over the combination of Clarke and Waksman in a Final Office Action dated 12 June 2006. The Appellant subsequently held an interview with Examiner Shay, and the corresponding Interview Summary dated 22 September 2006 indicates Examiner Shay agreed that the amended claim language overcomes the rejection based on the combination of Clarke and Waksman. However, Examiner Shay then issued another Office Action dated 11 July 2007 rejecting the claims over the combination of Clarke, James and Regunathan. The Appellant held another interview with Examiner Shay, which resulted in the Interview Summary mailed 2 November 2007 in which Examiner Shay indicated the amended claim language overcomes the rejection based on Clarke, James and Regunathan. Examiner Shay subsequently reversed his agreement and rejected the claims over the combination of Clarke, James and Regunathan in an Office Action dated 4 April 2008. On 30 June 2008, the Appellants held yet another interview with Examiner Shay and presented the Examiner with a draft of a declaration under 37 C.F.R. § 1.132 by Dr. Michael D. Laufer. The Interview Summary dated 30 June 2008 indicates agreement was reached that the pending claims now on appeal overcome the rejection based upon Clarke, James and Regunathan. Yet, in the Office Action dated 16 January 2009, Examiner Shay rejected these claims over the combination of Clarke, James, Regunathan and Waksman. As a result, prosecuting this application before Examiner Shay has required a considerable amount of energy, time, and money to address the inconsistent handling of the present application as evidenced by the record.

In addition to the inconsistent handling of this application, the 16 January 2009 Office Action includes assertions by Examiner Shay that incorrectly characterize statements made by the Appellant during the 30 June 2008 personal interview. A detailed response to Examiner Shay's incorrect characterization of the Appellant's statements during the 30 June 2008 personal interview is provided in the Amendment dated 13 May 2009. In short, Examiner Shay's recollections were written more than six months after holding the 30 June 2008 personal interview, and they are inaccurate.

The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and MPEP § 1205.2:

I.	Real Party In Interest
II	Related Appeals and Interferences
III.	Status of Claims
IV.	Status of Amendments
V.	Summary of Claimed Subject Matter
VI.	Grounds of Rejection to be Reviewed on Appeal
VII.	Argument
VIII.	Claims
Appendix A	Claims
Appendix B	Evidence
Appendix C	Related Proceedings

I. REAL PARTY IN INTEREST

The real party in interest is Asthmatx, Inc., the assignee of record of all right, title and interest in the present application.

II. RELATED APPEALS AND INTERFERENCES

An appeal is pending in U.S. Application No. 10/810,276, which claims priority to the present application. Neither Appellant, Appellant's legal representative, nor the above-identified Assignee are aware of any other appeals or interferences that are related to, will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 21 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 1-28, 38-49 and 51
2. Claims withdrawn from consideration but not canceled: None
3. Claims pending: 29-37, 50 and 52-62
4. Claims allowed: None
5. Claims rejected: 29-37, 50 and 52-62

C. Claims On Appeal

The claims on appeal are claims 29-37, 50 and 52-62

IV. STATUS OF AMENDMENTS

Appellant filed an Amendment on 22 July 2008. These amendments were considered and no new matter objections or rejections were raised in a Non-Final Action dated 16 January 2009. The Appellant also filed an Amendment on 13 May 2009 along with the Notice of Appeal in which claim 55 was amended to provide the proper antecedent basis for an element. The Examiner has not issued an Advisory Action in response to the Amendment filed on 13 May 2009.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A. Overview of Appellant's Technology

The subject matter defined by the claims involved in the present appeal is directed to a method and apparatus for treating asthma.

B. Claims on Appeal

Each claim being appealed is paraphrased below, with citations to the corresponding portions of the specification and drawings as required by 37 C.F.R. § 41.37(c)(1)(v). These citations are provided in order to illustrate specific examples and embodiments of the recited claim language, and are not intended to limit the claims.

1. Claim 29

Claim 29 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, wherein the irradiating step is performed by emitting a light energy having a wavelength of about 240 nm to about 280 nm. (Specification at, for example, p. 7, ln. 15.)

2. Claim 30

Claim 30 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, wherein the irradiating step is performed by emitting light energy having a wavelength in the red visible range. (Specification at, for example, p. 7, ln. 15.)

3. Claim 31

Claim 31 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, wherein the irradiating step is performed by exposing the walls to radiation emitted by a radioactive pellet. (Specification at, for example, p. 9, ln. 28 to p. 10, ln. 10.)

4. Claim 32

Claim 32 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, wherein the irradiating step is performed by moving an energy delivery device along the airway. (Specification at, for example, p. 7, ll. 5-11; p. 10, ll. 8-13.)

5. Claim 33

Claim 33 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, wherein irradiating walls of the airway also causes debulking over time in mucus gland cells and prevents the mucus gland cells from replicating. (Specification at, for example, p. 6, ll. 20-23; p. 10, ll. 25-28.)

6. Claim 34

Claim 34 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 33, wherein the irradiating step is performed by emitting a light energy having a wavelength of about 240 nm to about 280 nm. (Specification at, for example, p. 7, ln. 15.)

7. Claim 35

Claim 35 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 33, wherein the irradiating step is performed by emitting a light energy having a wavelength in a red visible range. (Specification at, for example, p. 7, ln. 15.)

8. Claim 36

Claim 36 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 33, wherein said irradiating step is performed by exposing the walls to radiation emitted by a radioactive pellet. (Specification at, for example, p. 9, ln. 28 to p. 10, ln. 10.)

9. Claim 37

Claim 37 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 33, wherein the irradiating step is performed by moving an energy delivery device along the airway. (Specification at, for example, p. 7, ll. 5-11; p. 10, ll. 8-13.)

10. Claim 50

Claim 50 is directed to a method for treating asthma to relieve asthmatic symptoms that includes providing a source of energy and irradiating walls of an airway of an asthmatic lung with the source of energy. (Specification at, for example, p. 4, ll. 1-3; p. 5, ll. 25-27; p. 6, ln. 12 to p. 11, ln. 9.) The airway is irradiated at a wavelength and intensity which, over time, causes debulking of smooth muscle tissue of the asthmatic

lung and prevents the lung tissue from replicating. (Specification at, for example, p. 6, ll. 6-20; p. 7, ll. 15-20; p. 10, ll. 25-28; p. 11, ll. 5-9.) Additionally, the irradiating procedure is performed by irradiating smooth muscle tissue in the asthmatic lung such that the ability of the airway to contract is reduced. (Specification at, for example, p. 11, ll. 5-9.)

11. Claim 52

Claim 52 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, further comprising placing a visualization system into the airway. (Specification at, for example, p. 6, ln. 24 to p. 7, ln. 2.)

12. Claim 53

Claim 53 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 52, wherein the visualization system comprises an endoscope or bronchoscope. (Specification at, for example, p. 6, ll. 27-29.)

13. Claim 54

Claim 54 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 32, wherein moving the energy delivery device along the airway comprises moving the energy delivery device in a uniform painting-like motion. (Specification at, for example, p. 7, ll. 5-11; p. 10, ll. 8-10.)

14. Claim 55

Claim 55 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 54, wherein moving the energy delivery device in the uniform painting-like motion comprises moving the entire energy delivery device either manually or by the motor. (Specification at, for example, p. 7, ll. 5-11.)

15. Claim 56

Claim 56 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, wherein irradiating walls of the airway with the source of energy comprises using an energy selected from a group consisting of infrared, visible, and ultraviolet. (Specification at, for example, p. 7, ll. 12-15.)

16. Claim 57

Claim 57 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 56, wherein irradiating walls of the airway with the source of energy comprises using incoherent light. (Specification at, for example, p. 7, ln. 12.)

17. Claim 58

Claim 58 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 56, wherein irradiating walls of the airway with the source of energy comprises using coherent light. (Specification at, for example, p. 7, ln. 12.)

18. Claim 59

Claim 59 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, wherein irradiating walls of the airway with the source of energy comprises irradiating the walls of the airway at an intensity sufficiently bright to penetrate mucus in the airway. (Specification at, for example, p. 7, ll. 16-19.)

19. Claim 60

Claim 60 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 50, further comprising delivering a photo-activatable substance to the airway. (Specification at, for example, p. 9, ll. 15-25.)

20. Claim 61

Claim 61 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 60, wherein the photo-activatable substance comprises a psoralen. (Specification at, for example, p. 9, ll. 15-25.)

21. Claim 62

Claim 62 is directed to a method for treating asthma to relieve asthmatic symptoms as set forth in claim 60, wherein an absorption spectrum of the photo-activatable substance is matched to the source of energy. (Specification at, for example, p. 9, ll. 15-25.)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. The Examiner's Rejections

1. The Examiner rejected claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, first paragraph.

2. The Examiner rejected claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, second paragraph.

3. The Examiner rejected dependent claims 30, 32, 33, 35, 37, 52, 53, 56, 58 and 59 under 35 U.S.C. § 102(b) over Ivanyuta et al., *Effect of Low-Power Laser Irradiation of Bronchial Mucosa on the State of Systemic and Local Immunity in Patients with Chronic Bronchitis* ("Ivanyuta").

4. The Examiner rejected claims 29, 32-34, 37, 50 and 56-59 under 35 U.S.C. § 103(a) over the combination of James et al., *The Mechanics of Airway Narrowing in Asthma* ("James"), U.S. Patent No. 5,053,033 ("Clarke"), International Publication No. WO97/37715 ("Waksman"), and U.S. Patent No. 5,574,059 ("Regunathan");

5. The Examiner rejected claims 30 and 35 under 35 U.S.C. § 103(a) over the combination of James, Clarke, Regunathan and U.S. Patent No. 5,422,362 ("Vincent");

6. The Examiner rejected claim 36 under 35 U.S.C. § 103(a) over the combination of James, Clarke, Regunathan and Waksman;

7. The Examiner rejected claims 52-55 under 35 U.S.C. § 103(a) over the combination of James, Clarke, Regunathan and U.S. Patent No. 5,458,596 ("Lax").

8. The Examiner rejected claims 60-62 under 35 U.S.C. § 103(a) over the combination of James, Clarke, Regunathan, U.S. Patent No. 6,008,211 ("Robinson"), and U.S. Patent No. 4,754,065 ("Levenson").

9. The Examiner rejected several different combinations of the pending claims under the doctrine of obviousness-type double patenting as being unpatentable over one or more claims of U.S. Patent Nos. 6,488,739 and 5,972,026, and U.S. Patent Application Nos.: 11/614,919; 11/612,620; 11/618,533; 11/609,242; 11/608,606; 11/617,512; 11/562,925; 11/425,345; 11/421,444; 11/398,353; 11/408,668; 11/420,442; 11/361,564; 11/117,905; 10/810,276; 11/562,910; 11/614,914; and 11/534,621.

B. The Issues on Appeal

1. Whether the Examiner erred in rejecting claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, first paragraph, based on claim language that is no longer applicable after the Amendment dated 22 July 2008.

2. Whether the Examiner erred in rejecting claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, second paragraph, based on claim language that is no longer applicable after the Amendment dated 22 July 2008.

3. Whether the Examiner erred in rejecting dependent claims 29, 32-34, 37, 50 and 56-59 over the combination of James, Clark, Waksman and Regunathan under 35 U.S.C. § 103.

4. Whether the Examiner erred in rejecting claims 30, 32, 33, 35, 37, 52, 53, 56, 58 and 59 under 35 U.S.C. § 102(b) over Ivanyuta.

5. Whether the Examiner erred in rejecting claims 29, 30, 32-35, 37, 50 and 52-59 under the doctrine of obviousness-typed double patenting over (a) U.S. Patent No. 6,488,739, which is not owned by the Appellant, (b) U.S. Patent No. 5,972,026 which is the subject of a Terminal Disclaimer already filed in this application, and (c) later filed U.S. Patent Application Nos. 11/614,919; 11/612,620; 11/618,533; 11/609,242; 11/608,606; 11/617,512; 11/562,925; 11/425,345; 11/421,444; 11/398,353; 11/420,442; 11/361,564; 11/117,905; 10/810,276; 11/562,910; 11/614,914; and 11/534,621.

VII. ARGUMENT

A. Section 112, Paragraph 1, Rejection of Claims 29-37, 50 and 52-62

1. Legal Standard for Written Description

35 U.S.C. § 112, first paragraph, requires that "The specification shall contain a written description of the invention." To satisfy the written description requirement, a patent specification "must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath ATH, Inc. v. Mahurkar*, 1135 F.2d at 1563, 19 USPQ2d at 1116; MPEP § 2163. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

2. The Examiner's Basis for Rejection

Claims 29-37, 50 and 52-62 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the phrase "such that the ability of smooth muscle to contract is reduced" in claim 50 was allegedly not described in the originally filed specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed." (16 January 2009 Office Action at p. 8, ln. 21, to p. 9, ln. 4, emphasis added.)

3. Appellant's Position

The rejection of claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, first paragraph, is improper because the Examiner based this rejection on language that was deleted from claim 50. In the Amendment dated 22 July 2008, the phrase "such that the ability of the smooth muscle to contract is reduced" was amended to read "such that the ability of the airway to contract is reduced." This amendment was discussed during the personal interview with the Examiner on 25 June 2008, and support for this feature is found, for example, at page 11, lines 5-9, of the originally filed specification. More specifically, this portion of the specification states "The elimination of smooth muscle tissue prevents the hyperactive airways of an asthma patient from contracting . . ." The specification accordingly provides express support for the phrase "such that the ability of the airway to contract is reduced." The Examiner never addresses the actual language of amended claim 50, but rather recycles a previous rejection of claim 50 before it was amended. Therefore, the Examiner erred in rejecting claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, first paragraph.

B. Section 112, Second Paragraph, Rejection of Claims 29-37, 50 and 52-62

Claims 29-37, 50 and 52-62 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. (16 January 2009

Office Action at p.9, ll. 8-13.) More specifically, the Examiner asserts that the phrase "such that the ability of the smooth muscle to contract is reduced" in claim 50 lacks positive antecedent basis in the originally filed disclosure. The Examiner erred again because this rejection is also based on language that is no longer in claim 50. Therefore, the rejection of claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, second paragraph, is improper.

Claim 55 was also rejected on the grounds that "the motor" lacks positive antecedent basis. Claim 55 was amended to read "a motor" in the Amendment filed on 13 May 2009. The Appellant respectfully submits that this amendment should have been entered because it does not change the scope of the claim and puts it in better condition for appeal. Therefore, the rejection of claims 29-37, 50 and 52-62 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

C. Section 103(a) Rejection of Claims 29, 32-34, 37, 50 and 56-59

1. Legal Standard for Obviousness

The Examiner has the initial burden of factually supporting any prima facie conclusion of obviousness under 35 U.S.C. §103 (a), which provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

To reach a proper determination under 35 U.S.C. § 103, "the Examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." MPEP § 2142. Although the tendency to resort to impermissible hindsight based upon the applicant's disclosure is often difficult to avoid, "impermissible hindsight must be avoided and the

legal conclusion must be reached on the basis of the facts gleaned from the prior art." Id.

In *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), the Supreme Court stated that an obvious analysis involves the following:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

More recently, in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the Supreme Court reaffirmed the holdings of Graham and clarified several aspects of the manner in which obviousness should be determined. First, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results," but "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious" (id. at 1739-40). Second, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art"; rather, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (id. at 1741). The Court recognized that many significant advances will combine familiar elements: "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known" (id).

Following the decision in *KSR Int'l*, the United States Patent and Trademark Office ("USPTO") issued a memorandum to all Examiners. The memorandum directs Examiners to continue to determine why a person of ordinary skill in the art would make the combination: "in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a

person of ordinary skill in the art would have combined the prior art elements in the manner claimed" (USPTO Memorandum, *Supreme Court decision on KSR Int'l. Co. v. Teleflex, Inc.*, May 3, 2007, p. 2). Furthermore, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Affidavits or declarations, when timely presented, containing evidence of skepticism of experts, etc., must be considered by the Examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. § 103. MPEP § 716.01(a). The weight attached to evidence of secondary considerations will depend upon its relevance to the issue of obviousness and the amount and nature of the evidence. MPEP § 716.01(b). When there is a factually and legally sufficient connection between the objective evidence of non-obviousness and the claimed invention so that the evidence is of probative value in the determination of non-obviousness, it is to be given substantial weight in the obviousness determination. Id. Additionally, "Expressions of disbelief by experts constitute strong evidence of non-obviousness." *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 715 F.2d 693, 698, 216 USPQ 865, 869 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1996)); MPEP § 716.05.

2. The Examiner's Basis

Claims 29, 32-34, 37, 50 and 56-59 were rejected under 35 U.S.C. § 103(a) over the combination of James, Clark, Waksman and Regunathan. The Examiner alleges that James teaches the mechanisms involved in airway narrowing in asthma include hypertrophy of smooth muscle; Regunathan teaches that restenosis is a result of hypertrophy of smooth muscle; Waksman teaches the equivalence of irradiation of the intima of bronchi and blood vessels to prevent hyperproliferation; and Clark teaches that restenosis can be treated by irradiation of a lumen wall with a laser having wavelengths in the claimed ranges to prevent the replication and growth of smooth muscle cells. The

Examiner then concludes that because James teaches hypertrophy is one of the mechanisms involved in airway narrowing in asthma, it allegedly would have been obvious to an artisan of ordinary skill to use the method of Clark for treating asthma on the bases that Waksman teaches bronchial smooth muscle cells and vascular smooth muscle cells are equivalent, and James and Regunathan teach both asthma and restenosis involve hypertrophy of smooth muscle cells. The Examiner further concludes it allegedly would have been obvious to move the device while irradiating because this would allow longer lesions for the treatment. (16 January 2009 Office Action at p. 9, ln. 16, to p. 10, ln. 6.)

With respect to the Declaration of Dr. Michael Laufer under 37 C.F.R. § 1.132 (the "Laufer Declaration"), the Examiner asserts that this declaration is not per se drawn to the claimed invention. The Examiner, more specifically, asserts that the Laufer Declaration is drawn to the knowledge of one of ordinary skill in the art at the time of the invention with respect to the motivation for combining James, Clarke, Waksman and Regunathan. (16 January 2009 Office Action at p.2, ll. 1-9.)

With regards to paragraphs 8 and 9 of the Laufer Declaration, the Examiner asserts that the facts and conclusions set forth in paragraph 8 are overly broad and that the facts set forth in paragraph 9 are not persuasive because of an alleged lack of context with regard to the method that was analyzed by the FDA. (16 January 2009 Office Action at p. 6, ln. 17, to p. 8, ln. 10.) The Examiner asserts that paragraph 10 of the Laufer Declaration merely provides an assertion of what a person of ordinary skill in the art would believe James to teach, and the Examiner dismisses this evidence stating that the rejection is not based on James in isolation. (16 January 2009 Office Action at p. 6, ll. 10-15.) Regarding paragraph 11 of the Laufer Declaration, the Examiner alleges that because James teaches the chronic inflammatory process present in the airway wall of patients is associated with cellular infiltration, deposition of connected tissue, hypertrophy of smooth muscle, goblet cell metaplasia of the epithelium, and an inflammatory exudate containing mucus in the airway movement, "to reverse the chronic

inflammatory process would require reversing smooth muscle cell hypertrophy and the excretion of mucus." (16 January 2009 Office Action at p. 6, ll. 16-22.)

With respect to paragraph 14, the Examiner asserts that hypertrophy can include hyperplasia on the grounds that the definition of hyperplasia in Stedman's Medical Dictionary, 26th Edition, is "an increase in the number of cells in a tissue or organ, excluding tumor formation, whereby the bulk of the part or organ may be increased. SEE ALSO, hypertrophy." (16 January 2009 Office Action at p. 7, ll. 1-9.) The Examiner further asserts that hypertrophy can include hyperplasia on the basis that James allegedly states both the production of connected tissue and smooth muscle cell hypertrophy are separate consequences of the inflammatory process which is to be reversed. (16 January 2009 Office Action at p. 7, ll. 9-12.) The Examiner then equates hyperplasia with hypertrophy for combining the method of Clarke with James.

With regard to paragraph 15 of the Laufer Declaration, the Examiner dismisses Dr. Laufer's statement that a person of ordinary skill in the art would not apply the methods of Clark and Regunathan to debulk airway smooth muscle tissue on the grounds that James refers to a purported hyperplasia meaning of the term hypertrophy. (16 January 2009 Office Action at p. 7, ll. 12-15.) With respect to paragraph 17 in the Laufer Declaration, the Examiner dismisses Dr. Laufer's statement that the increase in airway thickness in asthma is due to hypertrophy, rather than hyperplasia, on the grounds that this statement is not convincing in view of the Examiner's reading of James; the Examiner similarly dismisses the statements in paragraph 18 of the Laufer Declaration as being based on an erroneous interpretation of James. (16 January 2009 Office Action at p. 7, ll. 15-20.)

3. Appellant's Position

a. The Laufer Declaration

The Examiner's assessment of the Laufer Declaration is replete with errors including several instances where the Examiner substitutes his erroneous readings of the prior art for Dr. Laufer's knowledge as a person skilled in the art at the time of the invention. The Laufer Declaration should be given significant patentable weight even though Dr. Laufer is an interested party because it is supported by extrinsic evidence and Dr. Laufer has been a person of ordinary skill in the art since before 1998. The Laufer Declaration should also be given significant patentable weight because it is indeed drawn to the claimed subject matter and, more particularly, the faults in the Examiner's interpretations of the references and conclusions. Evidence submitted in a declaration depends on the relevance to the issue of obviousness, and there is a sufficient nexus between the merits of the claimed invention and the evidence of secondary considerations when the evidence is of probative value in the obviousness determination. MPEP § 716.01(b).

Claim 50 is directed to a method for treating asthma to relieve asthmatic symptoms by irradiating walls of an airway of an asthmatic lung. The airways are irradiated at a wavelength and intensity such that, over time, sufficient debulking of smooth muscle tissue occurs and lung tissue is prevented from replicating so that the ability of the airway to contract is reduced. One feature of claim 50 is accordingly debulking of existing, uninjured smooth muscle tissue in an asthmatic lung in addition to preventing future replication of the lung tissue. The Laufer Declaration provides evidence that is probative to the obviousness determination because, *inter alia*, it provides extrinsic evidence that teaches away from debulking airway smooth muscle tissue. For example, the Examiner states James' teaching of the reversal of the chronic inflammatory process "would require reversing smooth muscle hypertrophy." (16 January 2009 Office Action at p. 6, ll. 16-22.) The Laufer Declaration, however,

establishes that James teaches many different mechanisms and areas of chronic asthmatic inflammation, but it does not require the reversal of any specific mechanism. (Laufer Declaration at paragraph 7.) The Laufer Declaration also established that James does not teach debulking or otherwise affecting smooth muscle tissue to reverse the inflammatory process associated with asthma, and that the United States Food and Drug Administration (USFDA) was so skeptical of debulking airway smooth muscle that it denied approval of doing so until 2005. (Laufer Declaration at paragraphs 7 and 9.) The Laufer Declaration also directly refutes several other assertions and unsupported conclusions concocted by the Examiner. Therefore, the Laufer Declaration provides highly probative evidence regarding the obviousness determination and should be accorded significant weight.

The Examiner erred in asserting that the Laufer Declaration is not per se drawn to the claimed invention. More specifically, the Examiner stated "the Laufer Declaration is not per se drawn to the claimed invention (as it only discusses a subset of the claimed invention wherein all smooth muscle cells are actually killed (see the Laufer Declaration at paragraph 8, last sentence)[])]." (16 January 2009 Office Action at p.2, ll. 6-9.) In contrast to the Examiner's position, the last sentence of paragraph 8 of the Laufer Declaration is not limited to situations where all smooth muscle cells are killed, but rather this sentence reads "Therefore, in 1998, a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose and that airway smooth muscle cells should not be killed." Nothing in the last sentence of paragraph 8 of the Laufer Declaration describes a situation that is limited to killing all of the airway smooth muscle cells. The Laufer Declaration establishes, *inter alia*, that a person skilled in the art at the time of the invention would have understood that airway smooth muscle cells should not be killed to the extent that the lack of larger airway smooth muscle tone could impede the functional purpose that airway smooth muscle was thought to perform in normal lung function at the time of the invention (see, e.g., paragraphs 8 and 9 of the Laufer Declaration). The Laufer Declaration accordingly

discusses the understanding of a person skilled in the art at the time of the invention regarding the controversy surrounding the destruction or removal of airway smooth muscle as covered by the "debulking" element of claim 50. Thus, the Laufer Declaration is per se drawn to the claimed invention.

The Examiner also erred in dismissing the statement that the prevailing view at the time of the invention was airway smooth muscle had a functional purpose. Paragraph 8 of the Laufer Declaration cites two independent articles that show the early body of literature dating back over 125 years taught airway smooth muscle had one or more functional purposes. The Declarant states "Although Mitzner cites later articles as refuting some of the functional purposes of airway smooth muscle, Mitzner also points out that other listed functional purposes were still thought to be valid as late as 2004 (e.g., peristalsis to assist exhalation)." (Laufer Declaration at paragraph 8.) Thus, Dr. Laufer's statement that "a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose as of 1998" is fully supported by the cited articles. Moreover, as a doctor in the field at that time, Dr. Laufer's statement is uncontested by any factual evidence presented by the Examiner.

The Examiner further erred with respect to paragraph 8 of the Laufer Declaration in stating that the Laufer Declaration "would seem to indicate that one of ordinary skill in the art would believe that not even the death of a single airway smooth muscle cell could be tolerated, however, the instant claims are of such breadth that they would read on a procedure where only a small number of cells are killed." (16 January 2009 Office Action at p. 5, ll. 18-23.) In contrast to the Examiner's statement, the Laufer Declaration does not state that a person of ordinary skill in the art at the time of the invention would have believed that not even the death of a single airway smooth muscle cell could be tolerated. The Laufer Declaration consistently states "a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose and that airway smooth muscle cells should not be killed." (Emphasis added.) Dr. Laufer clearly used the plural term "cells" in direct opposition to the Examiner's unfounded assertion.

Moreover, it is clear from paragraphs 8 and 9 of the Laufer Declaration that Dr. Laufer addressed the situation of debulking airway smooth muscle where more than a single muscle cell was killed.

Paragraph 9 of the Laufer Declaration establishes that experts were skeptical about debulking airway smooth muscle tissue at the time of the invention. More specifically, irrespective of the methodology for debulking airway smooth muscle, the USFDA did not grant Asthmatx, Inc. approval to treat asthma in a human patient by debulking airway smooth muscle tissue using RF energy or any other modality until 2005. The redacted portion of a letter from James E. Dillard, III, director of the Division of Cardiovascular and Respiratory Devices in the Office of Device Evaluation of the United States Food and Drug Administration, read:

> Of concern is that ablation of airway smooth muscle and small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway broncospasm and then be unable to effectively cough and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways, coupled with underlying asthma, could lead to complications such as bronchiectasis.

The quoted language from Mr. Dillard stands for the proposition that the "lack of larger airway smooth muscle tone" (i.e., the debulked airway smooth muscle tissue) and the concomitant "reduced smooth muscle support of the conducting airways" associated with the debulking could lead to undesirable complications. Mr. Dillard took the position that airway smooth muscle has a functional purpose (e.g., dilation and restriction), and that it should not be reduced in size. The Examiner dismissed this evidence on the grounds that there was no context of the device or method that the USFDA analyzed and thus it was "impossible" to draw an inference of the knowledge of a person skilled in the art. The Examiner misses the point of paragraph 9 of the Laufer Declaration and the excerpt from the USFDA letter. The point is this: The premier U.S. Government

Agency on the topic believed (a) that airway smooth muscle was thought to perform an important function and (b) it would be undesirable to reduce the size of airway smooth muscle in asthma patients irrespective of the energy modality. Therefore, paragraph 9 of the Laufer Declaration and the excerpt from the USFDA should be given considerable weight.

Paragraph 10 of the Laufer Declaration establishes that James teaches the increase in airway wall thickness associated with asthma is not confined to the airway smooth muscle, but rather inflammation of the submucosa and the epithelium as well. This is directly from James and is incontrovertible. (James at p. 245, col. 1.) Paragraph 10 of the Laufer Declaration also establishes that James does not teach any specific mechanism to reverse the inflammatory progression in the airway wall. Although James teaches the inflammatory process should be reversed, James also teaches that there are many other causes of the inflammatory process besides smooth muscle hypertrophy and the inflammation is in other areas than the smooth muscle. (See, e.g., James at p. 245, col. 2, and p. 246, col. 1.) James does not teach which of the several listed causes should be treated to reverse the inflammation. Therefore, in light of the evidence from paragraphs 8 and 9 of the Laufer Declaration, Dr. Laufer correctly summarizes that a person skilled in the art would not understand James to mean that asthma should, or then could, be treated by debulking the airway smooth muscle as opposed to reversing any of the other causes or areas of inflammation set forth by James.

Paragraph 14 of the Laufer Declaration states that restenosis in vascular structures is caused by hyperplasia as opposed to hypertrophy of smooth muscle cells. Additionally, Dr. Laufer states hyperplasia in vascular applications is the excessive proliferation of new or additional cells above the level of normal cell production, whereas hypertrophy is the increase in size of existing cells without necessarily increasing the number of cells above normal levels. In contrast to the Examiner's assertion the difference between hyperplasia and hypertrophy is further supported by the definitions

of these terms in Stedman's Medical Dictionary, 27th Edition (2000). Although the Examiner's quote of Stedman's definition of hyperplasia is accurate, the Examiner read "SEE ALSO hypertrophy" as being synonymous. This is incorrect. Stedman's defines hypertrophy as a "general increase in bulk of a part or organ, not due to tumor formation. Use of the term may be restricted to denote greater bulk through increase in size, but not in number of cells or other individual tissue elements." Stedman's accordingly supports defining hyperplasia and hypertrophy as two distinct mechanisms such that hypertrophy does not include hyperplasia. Moreover, James consistently uses the terms hyperplasia and hypertrophy separately to mean separate conditions.

With regard to paragraph 15 of the Laufer Declaration, Dr. Laufer correctly states that neither Regunathan nor Clarke teaches debulking or otherwise removing uninjured vascular smooth muscle tissue that existed before an injury. Both of these references are clear that the restenosis treated by their methods is caused by hyper-proliferation. Dr. Laufer also notes that vascular smooth muscle provides an essential function for maintaining blood pressure through vasoconstriction and vasodilation such that a person skilled in the art would not apply the methods taught by Regunathan or Clarke in a manner that would debulk existing vascular smooth muscle tissue.

b. Meaning of the Cited References

James describes mechanics of airway narrowing in asthma patients. James teaches that the airway walls of asthma patients are thickened by chronic inflammation and concludes that such thickening of the airway walls could be as important as smooth muscle shortening in determining the airway responsiveness of these patients. (James at Summary.) James indicates that the airways of the asthmatic patients showed infiltration with inflammatory cells, thickening of the basement membrane, mucous gland and goblet cell prominence, and partial occlusion of the lumen with mucus and cellular debris. (James at p. 243, col. 3.) In addition, James discloses marked folding of the epithelium in some airways with a prominent circular layer of muscle. (James at p. 243,

col. 3 to 244, col. 1.) The increase in wall thickness, therefore, is not confined to the airway smooth muscle, but rather it also includes the submucosa and epithelium. (James at p. 245, col. 1.) James, for example, teaches that the chronic inflammatory process present in the airway wall in patients with asthma is associated with (a) cellular infiltration, (b) deposition of connective tissue, (c) goblet cell metaplasia of the epithelium, and (d) an inflammatory exudate containing mucus in the airway lumen in addition to hypertrophy of smooth muscle. (James at p. 246, col. 1.) James further teaches that an important feature of asthma treatments at that time was the rapid reversibility of airway obstruction with drugs that relax smooth muscle. (James at p. 245, col. 3.) According to James, bronchodilation does not need to be limited to reversal of excessive smooth muscle contraction, but rather reversing the muscle contraction can also be applied for non-excessive muscle contraction of thickened airway walls to increase airway caliber and lower the resistance to a similar degree. (James at p. 245, col. 3.) Based on these findings, James concludes that changes produced by chronic inflammatory processes can lead to excessive airway narrowing without excessive smooth muscle contraction such that the treatment of asthma should focus on (a) reversing the inflammatory changes in the airway wall and (b) relaxation of the airway smooth muscle. (James at p. 246, col. 1.)

Regunathan discloses that vascular hyperplasia, i.e., the excessive proliferation and hypertrophy of vascular smooth muscle cells, is a major pathogenic mechanism contributing to vascular pathology in atherosclerosis, hypertension resulting from renal artery stenosis and other causes, restenosis of coronary and other arteries after coronary angioplasty, insertion of vascular stents, and other conditions. (Regunathan at 1:17-27.) The invention of Regunathan is directed to a non-invasive method of inhibiting the initiation or progression of vascular hyperplasia and, in particular, to inhibiting proliferation of vascular smooth muscle cells. (Regunathan at 1:34-37.) Regunathan, more specifically, teaches a method of inhibiting the proliferation of vascular smooth muscle cells by administering a vascular smooth muscle cell anti-

proliferative effective amount of an I_2 imidazoline receptor agonist. (Regunathan at 1:37-42.)

Clarke is directed toward inhibiting restenosis associated with angioplasty and teaches that intimal hyperplasia or proliferation of vascular smooth muscle cells is a major factor in restenosis. (Clarke at 1:1-5 and 1:41-43.) Clarke further teaches vascular smooth muscle cells enter their growth cycle 2-3 days after injury and the majority of the vascular smooth muscle cells cease to proliferate within 7 days after injury. (Clarke at 1:43-50.) Clarke indicates that the total number of smooth muscle cells reaches a peak about two weeks after injury and remains constant for up to one year; Clarke states this suggests that a reduction of the number of smooth muscle cells injured during angioplasty will reduce the likelihood of subsequent restenosis. (Clarke at 1:50-55.) To inhibit restenosis, Clarke teaches reducing the proliferation of additional vascular smooth muscle cells in the blood vessel walls at an angioplasty site by irradiating the angioplasty site with the appropriate radiation in the UV wavelength range. (Clarke at 2:39-44.) The irradiation kills a major portion of the injured smooth muscle cells in the media so that few, if any, smooth muscle cells remain in the angioplasty site to proliferate and cause restenosis. (Clarke at 5:1-9.) However, as shown in Figures 3B and 3C, the thickness of media is not reduced by the process.

Waksman discloses an apparatus for delivering radioactive treatment from a radionuclide to tissue that has been damaged. Waksman teaches that the healing process in response to an injury is an overgrowth of tissue caused by increased cell proliferation that renarrows the lumen. (Waksman at 1:17-20.) In particular, Waksman teaches applying radiation from a radionuclide to prevent or inhibit hyperplasia following a balloon angioplasty procedure. (Waksman at 5:13-18 and 6:19-25.) Waksman provides a long list of vascular applications and also a list of non-vascular applications, including the bronchi in lungs, in which his invention may be useful. (Waksman 5:18-6:5.) However, in all of the applications disclosed in Waksman, his invention is directed toward inhibiting the proliferation of additional cells at an area that has been injured

during an earlier procedure. Waksman, moreover, does not disclose anything with respect to mucus or mucus gland cell debulking.

c. A Person of Ordinary Skill in the Art at the Time of the Invention Would Not Have Applied the Method of Clarke in an Asthmatic Lung For Treating Asthma Nor Have Understood That It Would Have Been Obvious to Try the Method of Clarke in Such a Manner

The rejection of claim 50 over the combination of James, Clarke, Waksman and Regunathan is improper because the Examiner incorrectly concludes that James' teachings require the reversal of airway smooth muscle hypertrophy and that the teachings of the other references would lead a person of ordinary skill in the art to apply the method in Clarke to reverse inflammation of airway smooth muscle to treat asthma. James teaches that the chronic airway inflammation of asthma is associated with several different factors including (a) cellular infiltration, (b) deposition of connective tissue, (c) goblet cell metaplasia of the epithelium, (d) hypertrophy of smooth muscle, and (e) an inflammatory exudate containing mucus in the airway lumen. (James at p. 246, column 1.) James further teaches that the inflammation occurs in several areas including the airway smooth muscle, the epithelium and the submucosa. (James at p. 245, column 1.) James concludes that the treatment should focus on both (a) reversing the inflammatory changes in the airway wall and (b) relaxation of the airway smooth muscle, but James does not teach which specific causes of the inflammation or which specific areas of the inflammation should be treated. (James at p. 246, column 1.) James, moreover, does not teach or otherwise suggest anything regarding how any of the listed causes should be treated other than drug treatments. James clearly does not teach any mechanism to debulk airway smooth muscle tissue. (Laufer Declaration at paragraph 10.) Therefore, to support this rejection, the Examiner must show (a) that a person skilled in the art in 1998 would select debulking airway smooth muscle as the mechanism to reverse the chronic inflammation taught by James,

and (b) that Clarke's process would be used for debulking uninjured, hypertrophied airway smooth muscle.

The Examiner fails to establish that a person skilled in the art at the time of the invention would have selected debulking airway smooth muscle to treat asthma. The Examiner uses only James for the proposition that a person skilled in the art would in fact reduce airway smooth muscle mass for treating asthma. However, the prevailing view at the time of the invention was that airway smooth muscle tissue performed an important functional purpose for normal lung function and that debulking airway smooth muscle could impair the normal lung function in an asthmatic lung. For example, the USFDA believed that airway smooth muscle facilitated airway dilation such that the lack of airway smooth muscle tone caused by debulking could render asthma patients unable to cough or clear secretions during exercise or other sympathetic stimulation. (Laufer Declaration at paragraph 9 citing USFDA letter dated 16 February 2001 regarding IDE no. G010016.) This was the reason why the USFDA initially denied approval of an Asthmatx device that reduced the airway smooth muscle tone (i.e., debulked smooth muscle) via ablation. Notably, the USFDA was not concerned about the mechanism (e.g., ablation), but rather the concern was the reduction in smooth muscle tone. Also, Paragraph 8 of the Laufer Declaration provides factual evidence that other experts in the art recognized that airway smooth muscle tissue performed a functional purpose for normal lung function. This evidence accordingly establishes that third party experts in the field at the time of the invention thought that airway smooth muscle performed an important functional purpose, and that it should not be debulked for fear of further impairing lung function in an asthmatic patient. Therefore, there is significant evidence that a person skilled in the art would not select debulking airway smooth muscle even in light of James' teachings.

The Examiner erred by completely dismissing the statement from the USFDA on the grounds that it purportedly lacked any context with regard to the claimed method. The Examiner is incorrect and misses the point - the USFDA's statement is highly

probative because it establishes that the foremost U.S. Government Agency in the field was skeptical about debulking airway smooth muscle tissue to treat asthma at the time of the invention. The statement from the USFDA regarding the size and tone of airway smooth muscle is not only directly on point, but it comes from a government agency that has far more expertise in the relevant art than the Examiner. The articles cited in paragraph 8 of the Laufer Declaration further support the view that airway smooth muscle was thought to perform an important function at the time of the invention. Therefore, in light of all the evidence to the contrary, the Examiner's assertion that in 1998 a person skilled in the art would consider reducing airway smooth muscle to be a medically acceptable option for treating asthma is incorrect.

The Examiner also fails to establish that Clarke's process for preventing excessive growth of new cells in response to a vascular injury would be used to debulk uninjured, hypertrophied airway cells. To reach this conclusion, the Examiner argues that hypertrophy can include hyperplasia and that James uses the terms hypertrophy and hyperplasia interchangeably. The Examiner's analysis, however, does not comport with the use of hyperplasia and hypertrophy set forth in the cited references, Stedman's Medical Dictionary (27th Edition), or the understanding of a person of ordinary skill in the vascular space. Starting with Regunathan, although this reference states that "vascular hyperplasia, i.e., the excessive proliferation and hypertrophy of VSM cells" is a major pathogenic mechanism contributing to vascular pathology in restenosis, Regunathan describes treating disorders by administering a vascular smooth muscle anti-proliferative pharmacological agent. (Emphasis added.) The treatment described in Regunathan is accordingly directed to limiting excessive proliferation of vascular cells (i.e., hyperplasia) as opposed to reducing the preexisting size of the VSM cells (i.e., hypertrophy). (Laufer Declaration at paragraph 12.) These terms are not interchangeable in the vascular space, and the Examiner cannot be allowed to pick and chose from an inaccurate usage of these terms. Therefore, Regunathan does not teach reducing the size of existing, uninjured smooth muscle cells (i.e., hypertrophy).

Clarke is also directed toward inhibiting restenosis associated with hyperplasia caused by a vascular injury (i.e., by reducing the proliferation of additional vascular smooth muscle cells). (Laufer Declaration at paragraph 13.) Clarke does not mention hypertrophy, but instead uses hyperplasia to mean the proliferation of new smooth muscle cells in response to an injury. As such, based on the entire teachings of Clarke and Regunathan, a person skilled in the art at the time of the invention would have understood that the purpose of both Regunathan and Clarke was to inhibit the production of additional vascular smooth muscle cells that would normally incur in response to damage, injury or other trauma to the vessel wall. (Laufer Declaration at paragraph 14.)

James consistently states that the chronic inflammation associated with asthma is caused by several factors including "smooth muscle hypertrophy." James mentions hyperplasia in the context of citing an article by Heard and Hosain stating "Heard and Hosain (9) showed that this [increase in smooth muscle in the major bronchi] was due to hyperplasia rather than hypertrophy. The present study confirms an increase in smooth muscle volume as well as an increase in the volume of the nonmuscular wall components." The Heard and Hosain article clearly distinguishes between hyperplasia and hypertrophy. James merely states that his study confirms an increase in smooth muscle volume, but James did not confirm that the cause was hyperplasia. Instead, James consistently stated that the increase in smooth muscle volume was caused by hypertrophy. Given that Heard and Hosain were clear that these terms have different meanings and that James consistently used only hypertrophy, the best reading of James to a person skilled in the art is that James used hypertrophy to refer to a different condition than hyperplasia.

In putting the teachings of these three references together, it accordingly starts with James' teaching that the chronic inflammation associated with asthma is caused, in part, by smooth muscle hypertrophy. This type of tissue growth is different than the growth caused by proliferation of new cells. For example, unlike a proliferation of new

cells in response to an injury, enlargement of uninjured preexisting cells is caused by use (e.g., muscle growth through exercise). Neither Regunathan nor Clarke teaches debulking or otherwise reducing uninjured vascular smooth muscle tissue that existed before an injury or other trauma occurred. Therefore, a person of ordinary skill in the art would not use Clarke's method to irradiate an uninjured airway wall of an asthmatic lung at a wavelength and intensity that, over time, would debulk airway smooth muscle based on the teachings of James, Regunathan or Clarke, either individually or collectively. (Laufer Declaration at paragraph 18.)

The addition of Waksman to the combination of James, Regunathan and Clarke does not provide the missing elements from James, Regunathan or Clarke. The Examiner sites Waksman for the proposition that this reference teaches irradiating blood vessels is equivalent to irradiating the intima of bronchi to prevent hyperproliferation. (16 January 2009 Office Action at p. 9, ll. 20-21.) This assertion by the Examiner is incorrect because vascular structures and airway structures are significantly different from each other. For example, the airway epithelium is comprised of tight junctions of columnar cells that are 10-15 times thicker than the single flat layer of squamous cells that comprise the vascular endothelium. (Laufer Declaration at paragraph 19.) The airway epithelium also necessarily facilitates diffusion of nitrogen for proper lung function, but the vascular endothelium prevents diffusion of nitrogen and nitrogen-containing substances (e.g., nitrogen monoxide in particular) because these gases have a direct effect on causing vascular smooth muscle to contract. (Laufer Declaration at paragraph 19.) The prevention of diffusion of nitrogen and nitrogen-containing substances could be catastrophic in an airway. (Laufer Declaration at paragraph 19.) The airway epithelium and blood vessel endothelium are accordingly two different materials with different properties that react differently to irradiation. As a result, the intensity of UV radiation to prevent the hyperproliferation of vascular smooth muscle cells in response to angioplasty in a blood vessel does not inherently debulk uninjured airway smooth muscle through the epithelium of an airway. (Laufer

Declaration at paragraph 19.) The broad assertion that Waksman teaches irradiating the intima of bronchi is equivalent to irradiating blood vessels to prevent hyperproliferation is accordingly incorrect. Therefore, the addition of Waksman does not overcome the shortcoming of the combination of James, Clarke and Regunathan.

Moreover, even if Waksman arguably teaches equivalence between irradiating the intima of bronchi and irradiating blood vessels to prevent hyperproliferation in response to an injury, Waksman still does not teach any equivalence between irradiating uninjured vascular or airway smooth muscle tissues. A person of ordinary skill in the art at the time of the invention accordingly would not consider Waksman to teach a reason to irradiate an uninjured airway wall of an asthmatic lung at a wavelength and intensity that, over time, would debulk airway smooth muscle. Therefore, even when combined, the cited combination of references fails to teach all of the claimed elements.

d. Even If the References are Properly Combined, Which the Appellant Does Not Concede, the Cited Combination of References Does Not Teach All of the Elements of Claim 50

Claim 50 is patentable over the cited combination of references because none of these references teaches a process that debulks uninjured hypertrophied airway smooth muscle tissue. As noted above, both Regunathan and Clarke only teach methods for inhibiting the proliferation of additional smooth muscle cells that occurs in response to a vascular injury. (Laufer Declaration at paragraph 15.) Vascular smooth muscle, moreover, provides an essential function for maintaining blood pressure through vasoconstriction and vasodilation. (Laufer Declaration at Paragraph 15.) A person skilled in the art, therefore, would not apply the methods taught in Regunathan and/or Clarke in a manner that would debulk existing vascular smooth muscle tissue because this would reduce the smooth muscle tone. (Laufer Declaration at paragraph 15.) The rationale supporting Dr. Laufer's statement is similar to the rationale that the USFDA used to initially deny approval of Asthmatx's device because vascular smooth

muscle incontrovertibly performs an essential purpose. If a person of ordinary skill in the art would not apply the method taught by Clarke to treat uninjured hypertrophied vascular smooth muscle, then if follows that Clarke would not be applied to treat uninjured hypertrophied airway smooth muscle. As a result, if the cited references were combined and applied as set forth in the references, the resulting process would irradiate the airway smooth muscle at a wavelength and intensity that merely prevents the future proliferation of smooth muscle cells after an injury instead of debulking the existing uninjured smooth muscle tissue. The cited combination of references, therefore, fails to disclose or suggest all the features of claim 50.

e. Dependent Claims 33 and 59 Stand on Their Own for the Purposes for this Appeal Because These Claims are Further Patentable Over the Combination of James, Regunathan, Clarke and Waksman Under Section 103

Claim 33 is further patentable under Section 103 over the cited combination of references because claim 33 depends from claim 50 and further includes "wherein irradiating walls of the airway also causes debulking over time in mucus gland cells and prevents the mucus gland cells from replicating." The cited combination of references fails to teach anything with respect to debulking mucus gland cells or preventing the mucus gland cells from replicating. Moreover, the Examiner fails to identify any portion of the cited references that discloses this subject matter. Claim 33 is accordingly patentable over the cited combination of references for the reasons described above with respect to claim 50 and for the additional features of claim 33.

Claim 59 is also further patentable over the cited combination of references because this claim depends from claim 50 and further includes "wherein irradiating walls of the airway with the source of energy comprises irradiating the walls of the airway at an intensity sufficiently bright to penetrate mucus in the airway." As explained above with respect to claim 33, none of the cited references teaches anything with respect to irradiating the walls of the airway at an intensity sufficiently bright to penetrate mucus in

the airway. The Examiner also completely fails to identify any portion of the cited references that teaches the additional subject matter of claim 59. Therefore, claim 59 is patentable over the cited combination of references under Section 103 for the reasons explained above with respect to claim 50 and also because of the additional features of claim 59.

D. Section 102 (b) Rejection of Claims 30, 32, 33, 35, 37, 52, 53, 56, 58 and 59

1. Legal Standard for Anticipation

As with obviousness, the Examiner has the initial burden of factually supporting any prima facie conclusion of anticipation under 35 U.S.C. §102 (b). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131.

2. The Examiner's Basis

Claims 30, 32, 33, 35, 37, 52, 53, 56, 58 and 59 were rejected under § 102 over Ivanyuta. In making this rejection, the Examiner states that these claims are "clearly anticipated by Ivanyuta." The Examiner provides no further clarity as to the application of Ivanyuta to these claims.

Paragraphs 20 and 21 of the Laufer Declaration discuss Ivanyuta. With respect to paragraph 20 of the Laufer Declaration, the Examiner asserts that the basis for the statement "a person of ordinary skill in the art would not be motivated or otherwise think of applying radiation to effect a change in the airway mucus gland cells such that mucus secretions are reduced" is unclear. This language is not in paragraph 20 of the Laufer Declaration, and therefore it is the Examiner's assertion that is unclear. Regarding paragraph 21 of the Laufer Declaration, the Examiner asserts the following: (a)

Ivanyuta does not caution against treating individuals with chronic non-obstructive bronchitis that are also experiencing asthma; and (b) "since the disclosure of Ivanyuta et al provides for administering each step clamed [sic], in the method, any asthma that the patient was afflicted with would be treated." However, as explained in more detail below, Ivanyuta does not mention asthma and is only directed to chronic non-obstructive bronchitis.

3. Appellant's Position

a. The Laufer Declaration

Paragraphs 20 and 21 of the Laufer Declaration should be give significant patentable weight. Paragraph 20 accurately summarizes the relevant teachings of Ivanyuta - this was not traversed by the Examiner. Paragraph 21 sets forth why a person skilled in the art would not apply Ivanyuta's teachings that are directed specifically to chronic non-obstructive bronchitis to treat a patient having asthma. In response to the Examiner's assertions regarding paragraph 21 of the Laufer Declaration, Ivanyuta doesn't expressly caution against using his treatment with individuals that experience asthma because Ivanyuta fails to mention or suggest anything regarding asthma. It is not even disclosed whether any of Ivanyuta's subjects had asthma. Moreover, a person skilled in the art in 1998 would still not apply Ivanyuta for treating asthma to relieve asthmatic symptoms based on the prevailing view that airway smooth muscle had an important function in normal lung operation and the statements in Ivanyuta. More specifically, Ivanyuta states that after one or two treatments coughing intensified and sputum increased. (Ivanyuta at p. 3.) After an undisclosed period of time, Ivanyuta states that these signs of exacerbation went down: coughing stopped altogether (26% of the cases) or decreased significantly (68% of the cases); and the sense of tickling in the throat during breathing went away. (Ivanyuta at p. 3.) Additionally, an intensification of hyperemia of the bronchial mucosa and an increase in secretion in the bronchi lumen were also found. (Ivanyuta at p. 3.) All of

these exacerbating aspects of Ivanyuta's treatment were thought to be significant problems with asthma patients because asthma is an obstructive disease (see, e.g., the arguments above regarding the USFDA statement).

b. Meaning of the Cited Reference

Ivanyuta is directed to treating chronic non-obstructive bronchitis. Ivanyuta discloses that disruptions of local and systemic immunity are involved in chronic non-obstructive bronchitis. (Ivanyuta at 1.) Ivanyuta teaches that the efficacy of drugs many not satisfy clinical physicians and that lasers have been proven to affect the pathologic process and immunocompetent cells. (Ivanyuta at 1.) Ivanyuta studied the efficacy of endobronchial low-power laser therapy and its effect on the immune status of patients with chronic non-obstructive bronchitis. (Ivanyuta at 2.) More specifically, Ivanyuta irradiated the mucosa of the trachea and bronchi during fibrobronchoscopy using red light at a wavelength of 633 nm and a power of 6-8 mW at the light-guide exit. (Ivanyuta at 2.) The total dose applied during a session ranged from 2.1-3 J, and four to seven procedures were performed over a number of days. (Ivanyuta at 2.) Ivanyuta teaches that the patients exhibited the characteristic dynamics of bronchial lesions. (Ivanyuta at 2.) Ivanyuta states that some aggravation occurred after one or two procedures resulting in an initial intensification of coughing and increase of sputum; after an undisclosed time period, the coughing stopped or decreased significantly and the sense of tickling of the throat went away. (Ivanyuta at 3.)

c. Ivanyuta Fails to Disclose or Suggest All of the Features of Independent Claim 50 from which the Rejected Claims Depend

The rejection of dependent claims 30, 32, 33, 35, 37, 52, 53, 56, 58 and 59 over Ivanyuta is improper because Ivanyuta fails to disclose or suggest all of the features of claim 50. The claims subject to this rejection depend from claim 50, and therefore all of these claims include the preamble "A method for treating asthma to relieve asthmatic

symptoms." As explained above, Ivanyuta discloses treating only chronic non-obstructive bronchitis. Asthma, on the other hand, is an obstructive pulmonary disease that is completely distinct and different. The Examiner asserts that any asthma experienced by Ivanyuta's subjects with chronic non-obstructive bronchitis would have been treated by Ivanyuta's process. Ivanyuta, however, does not mention asthma or that any of his subjects had asthma. As such, Ivanyuta does not disclose that his method would relieve asthma symptoms. The Examiner simply makes up this hypothetical situation and uses it as a basis for the rejection. Therefore, Ivanyuta does not anticipate these claims for at least the reason that this reference does not disclose a method for treating asthma to relieve asthmatic symptoms.

Ivanyuta also fails to anticipate these dependent claims because Ivanyuta does not teach debulking the airway smooth muscle tissue such that the ability of the airway to contract is reduced. Ivanyuta is completely silent with respect to this feature of the dependent claims, and the Examiner does not provide any evidence that Ivanyuta's process would inherently debulk the airway smooth muscle. The Examiner asserts that Ivanyuta would inherently debulk the airway smooth muscle. However, Ivanyuta discloses only a low-power process and it is not clear whether his process would in fact debulk airway smooth muscle. Therefore, Ivanyuta also fails to anticipate this element of the claims.

The pending claims are also patentable over Ivanyuta under § 103 because a person of ordinary skill in the art would not irradiate an airway wall of an asthmatic lung to treat asthma based on Ivanyuta. First, Ivanyuta is directed to treating chronic non-obstructive bronchitis such that this reference is not directed to asthma or another chronic obstructive pulmonary disease. (Laufer Declaration at paragraph 21.) Second, Ivanyuta fails to provide any teaching regarding asthma and does not discuss either hypertrophy or hyperplasia. (Laufer Declaration at paragraph 21.) Third, a person of ordinary skill in the art, such as Mr. Dillard, III, from the USFDA, understood that airway smooth muscle was important for normal lung function at the time of the present

invention. (Laufer Declaration at paragraphs 8 and 9.) Fourth, Ivanyuta states that his procedure caused at least temporary coughing, increased sputum and tickling in the throat that are undesirable in asthma patients. (Ivanyuta at p. 3.) Ivanyuta also stated that further exacerbations of his treatment were intensification of hyperemia of the bronchial mucosa and an increase in secretion in the bronchi lumen. (Ivanyuta at p. 3.) Ivanyuta would not lead a person of ordinary skill in the art to irradiate an airway wall of an asthmatic lung to treat asthma in light of these factors. Therefore, claims 32, 33, 35, 37, 52, 53, 56, 58 and 59 are patentable over Ivanyuta under §§ 102 and 103.

d. Dependent Claims 29, 31, 34, 36, 57 and 60-62 Stand as Follows for the Purposes for this Appeal Because These Claims are Further Patentable Over Ivanyuta Under Sections 102 or 103

Claim 29 depends from claim 50 and further includes "wherein said irradiating step is performed by emitting a light energy having a wavelength of about 240 nm to about 280 nm." Claim 34 also includes the 240-280 nm wavelength element and further includes "wherein irradiating walls of the airway also causes debulking over time in mucus gland cells and prevents the mucus gland cells from replicating." In contrast to these claims, Ivanyuta discloses using monochromatic red light at a wavelength of 633 nm. Claims 29 and 34 are accordingly patentable over Ivanyuta for the reasons explained above with respect to claim 50 and also because of the additional features of these claims.

Claim 31 is patentable over Ivanyuta under Sections 102 and 103 because this claim depends from claim 50 and also because this claim includes "wherein said irradiating step is performed by exposing the walls to irradiation emitted by a radioactive pellet." Claim 36 has a similar feature and further includes the subject matter of claim 33. In contrast to these claims, Ivanyuta only discloses using a laser to provide irradiation at a wavelength of 633 nm. Claims 31 and 36, therefore, are patentable over

Ivanyuta under Sections 102 or 103 as depending from independent claim 50 and because of the additional features of these claims.

Claim 57 is further patentable over Ivanyuta under Sections 102 and 103 because this claim depends from claims 50 and 56, and claim 57 further includes "wherein irradiating walls of the airway with the source of energy comprises using incoherent light." Ivanyuta discloses using an AFL-1 laser that generates red light at a wavelength of 633 nm. A laser produces coherent light, and thus claim 57 is further patentable over Ivanyuta under Sections 102 and 103.

Claims 60-62 are further patentable over Ivanyuta under Sections 102 and 103 because these claims depend from claim 50 and further include "further comprising delivering a photo-activatable substance to the airway." Ivanyuta fails to disclose or suggest anything with respect to delivering a photo-activatable substance to the airway. Claim 61 further defines the photo-activatable substance comprises a psoralen, and claim 62 further defines the photo-activatable substance as having an absorption spectrum matched to the source of energy. Ivanyuta also fails to disclose or suggest anything with respect to these additional features of claims 61 and 62. Therefore, claims 60-62 are patentable over Ivanyuta under Sections 102 and 103 as depending from claim 50 and also because of the additional features of these dependent claims.

E. Obviousness-Type Double Patenting Rejections

1. The Examiner's Position

Claims 29, 30, 32-35, 37, 50 and 52-59 were rejected under the doctrine of obviousness-typed double patenting over (a) U.S. Patent No. 6,488,739, (b) U.S. Patent No. 5,972,026, and (c) later filed U.S. Patent Application Nos. 11/614,919; 11/612,620; 11/618,533; 11/609,242; 11/608,606; 11/617,512; 11/562,925; 11/425,345; 11/421,444; 11/398,353; 11/420,442; 11/361,564; 11/117,905; 10/810,276; 11/562,910; 11/614,914; and 11/534,621.

2. The Appellant's Position

The rejection of the pending claims over U.S. Patent No. 6,488,739 is incorrect because this patent is not owned by the Appellant. Moreover, U.S. Patent No. 6,488,739 is directed toward an "Oxygen Production Process" - not even remotely related to the subject matter of the claims in the present application. Therefore, this rejection is clearly incorrect.

The rejection of canceled claims 1 and 10 over U.S. Patent No. 5,972,026 is also incorrect. First, claims 1 and 10 have been canceled from the application. Second, a Terminal Disclaimer regarding U.S. Patent No. 5,972,026 was filed in this application on 31 October 2007 as explained to Examiner Shay in the Amendment filed on 22 July 2008. It appears that this rejection was inadvertently recycled from a previous Office Action because it is not relevant and is located at the very end of the 16 January 2009 Office Action after the normal closing paragraphs and apart from the rest of the rejections.

The provisional rejection of the pending claims over later filed U.S. Patent Application Nos. 11/614,919; 11/612,620; 11/618,533; 11/609,242; 11/608,606; 11/617,512; 11/562,925; 11/425,345; 11/421,444; 11/398,353; 11/420,442; 11/361,564; 11/117,905; 10/810,276; 11/562,910; 11/614,914; and 11/534,621 will be mooted if the present application is allowed to issue. The present application antedates all of the foregoing copending applications. Therefore, pursuant to MPEP § 804, if the present application is in condition for allowance before issuance of the listed copending applications, then the present application should not be subject to an obviousness-type double patenting rejection over those applications. The Appellant respectfully requests reversal of this rejection if the other rejections set forth above are reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A include the amendments filed by Applicant on November 11, 2008.

Dated: 13 August 2009

Respectfully submitted,

By _____

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 09/095,323

1-28. (Cancelled)

29. (Previously Presented) The method of Claim 50, wherein said irradiating step is performed by emitting a light energy having a wavelength of about 240 nm to about 280 nm.

30. (Previously Presented) The method of Claim 50, wherein said irradiating step is performed by emitting light energy having a wavelength in the red visible range.

31. (Previously Presented) The method of Claim 50, wherein said irradiating step is performed by exposing the walls to radiation emitted by a radioactive pellet.

32. (Previously Presented) The method of Claim 50, wherein said irradiating step is performed by moving an energy delivery device along the airway.

33. (Previously Presented) The method of claim 50, wherein irradiating walls of the airway also causes debulking over time in mucus gland cells and prevents the mucus gland cells from replicating.

34. (Original) The method of Claim 33, wherein said irradiating step is performed by emitting a light energy having a wavelength of about 240 nm to about 280 nm.

35. (Previously Presented) The method of Claim 33, wherein said irradiating step is performed by emitting a light energy having a wavelength in a red visible range.

36. (Original) The method of Claim 33, wherein said irradiating step is performed by exposing the walls to radiation emitted by a radioactive pellet.

37. (Original) The method of Claim 33, wherein said irradiating step is performed by moving an energy delivery device along the airway.

38-49. (Cancelled)

50. (Previously Presented) A method for treating asthma to relieve asthmatic symptoms, the method comprising:

providing a source of energy; and

irradiating walls of an airway of an asthmatic lung with the source of energy at a wavelength and intensity which, over time, causes debulking of smooth muscle tissue of the asthmatic lung and prevents the lung tissue from replicating, wherein said irradiating step is performed by irradiating smooth muscle tissue in the asthmatic lung such that the ability of the airway to contract is reduced.

51. (Cancelled)

52. (Previously Presented) The method of claim 50, further comprising placing a visualization system into the airway.

53. (Previously Presented) The method of claim 52, wherein the visualization system comprises an endoscope or bronchoscope.

54. (Previously Presented) The method of claim 32, wherein moving the energy delivery device along the airway comprises moving the energy delivery device in a uniform painting-like motion.

55. (Currently Amended) The method of claim 54, wherein moving the energy delivery device in the uniform painting-like motion comprises moving the entire energy delivery device either manually or by the motor.

56. (Previously Presented) The method of claim 50, wherein irradiating walls of the airway with the source of energy comprises using an energy selected from a group consisting of infrared, visible, and ultraviolet.

57. (Previously Presented) The method of claim 56, wherein irradiating walls of the airway with the source of energy comprises using incoherent light.

58. (Previously Presented) The method of claim 56, wherein irradiating walls of the airway with the source of energy comprises using coherent light.

59. (Previously Presented) The method of claim 50, wherein irradiating walls of the airway with the source of energy comprises irradiating the walls of the airway at an intensity sufficiently bright to penetrate mucus in the airway.

60. (Previously Presented) The method of claim 50, further comprising delivering a photo-activatable substance to the airway.

61. (Previously Presented) The method of claim 60, wherein the photo-activatable substance comprises a psoralen.

62. (Previously Presented) The method of claim 60, wherein an absorption spectrum of the photo-activatable substance is matched to the source of energy.

APPENDIX B

A copy of evidence pursuant to §§ 1.130, 1.131, or 1.132 and/or evidence entered by or relied upon by the examiner that is relevant to this appeal is attached hereto. A Declaration Under 37 C.F.R. § 1.132 of Dr. Michael D. Laufer was entered by the Examiner in the 16 January 2009 Office Action.

Declaration Under 37 C.F.R. § 1.132 of Dr. Michael D. Laufer.

Attachment 1

Declaration of Michael D. Laufer, M.D., Under 37 C.F.R. 1.132

Docket No.: 649218007US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: MICHAEL D. LAUFER	
APPLICATION NO.: 09/095,323	CONFIRMATION NO.: 9521
FILED: JUNE 10, 1998	ART UNIT: 3735
FOR: METHOD AND APPARATUS FOR TREATING SMOOTH MUSCLES IN THE WALLS OF BODY CONDUITS	EXAMINER: D. M. SHAY

Declaration of Michael D. Laufer, M.D., Under 37 C.F.R. 1.132

I, Michael D. Laufer, M.D., hereby declare and state.

1. I received a Bachelor of Arts degree from the University of Colorado at Boulder in 1980, and I received a Medical Doctorate degree from the Stanford University School of Medicine in 1985. My postdoctoral training included the following positions: Intern in Emergency Medicine at Harbor-UCLA from 1985-1986; Resident in Emergency Medicine at Harbor-UCLA from 1986-1988; and Fellow/Attending in Trauma, Surgery, Emergency Medicine and Pre-Hospital Care at Stanford University from 1988-1989.

2. I hold the following licenses and certifications:

   1983 Advanced Cardiac Life Support Instructor and Provider
   1983 Basic Life Support Instructor and Provider
   1986 Advanced Trauma Life Support Provider and Course Instructor
   1986 Basic Trauma Life Support Instructor
   1986 Pediatric Advanced Life Support Provider and Instructor
   1987 Certified Base Station Physician for Los Angeles and Santa Clara Counties
   1992 Board Certified - American College of Emergency Medicine
   1993 Fellow - American College of Emergency Physicians
   1994 Board Certified Forensic Medical Examiner

1995 Neonatal Advanced Life Support Provider
1997 Fellow - American College of Forensic Medical Examiners
1997 Affiliate Faculty - Northern California Basic Trauma Life Support
1987 California Medical License No. G59661, DEA BL0859249
1990 Nevada Medical License No. 6566

3. I have also held and/or hold the following academic positions:

2006-present	Instructor at Harvard Medical School Beth Israel-Deaconesse Medical Center Department of Surgery
1990-present	Clinical Instructor at Stanford University
1990-1995	Assistant Clinical Professor at University of California San Francisco Department of Medicine
1989-1990	Acting Assistant Professor at Stanford University School of Medicine Department of Surgery/Emergency Medicine

4. Since 1993, I have been involved in creating new medical devices to treat patients with common illnesses, and I have started more than 10 companies directed to over 15 new technologies. In 1997, I founded Broncus Technologies, Inc., and Asthmatx, Inc. became a separate company from Broncus Technologies, Inc. in December of 2003. I am currently a Board Member and a paid consultant for Asthmatx, Inc., and hold option and stock interest in Asthmatx, Inc.

5. With respect to the subject matter of U.S. Patent Application No. 09/095,323, a person of ordinary skill in the art has a Medical Doctorate degree and 6 or more years of experience in treating patients with chronic and/or acute asthma.

6. I have carefully reviewed James et al., *The Mechanics of Airway Narrowing in Asthma*, Amr. Rev. Respir. Dis. Volume 139:242-246 (1989) ("James"); U.S. Patent No. 5,574,059 ("Regunathan"); U.S. Patent No. 5,053,033 ("Clarke"); and Ivanyuta et al., *Effect of Low-Power Laser Irradiation of Bronchial Mucosa on the State of Systemic and Local*

Immunity in Patients with Chronic Bronchitis, Problemy Tuberkuleza No. 6:26-29 (1991) ("Ivanyuta").

7. James describes mechanics of airway narrowing in asthma patients. James teaches that the airway walls of asthma patients are thickened by chronic inflammation and concludes that such thickening of the airway walls could be as important as smooth muscle shortening in determining the airway responsiveness of these patients. (James at Summary.) James indicates that the airways of the asthmatic patients showed infiltration with inflammatory cells, thickening of the basement membrane, mucous gland and goblet cell prominence, and partial occlusion of the lumen with mucus and cellular debris. (James at p. 243, col. 3.) In addition, James discloses marked folding of the epithelium in some airways with a prominent circular layer of muscle. (James at p. 243, col. 3 to 244, col. 1.) The increase in wall thickness, therefore, is not confined to the airway smooth muscle, but rather it also includes the submucosa and epithelium. (James at p. 245, col. 1.) James, for example, teaches that the chronic inflammatory process present in the airway wall in patients with asthma is associated with (a) cellular infiltration, (b) deposition of connective tissue, (c) goblet cell metaplasia of the epithelium, and (d) an inflammatory exudate containing mucus in the airway lumen in addition to hypertrophy of smooth muscle. (James at p. 246, col. 1.) James further teaches that an important feature of asthma treatments at that time was the rapid reversibility of airway obstruction with drugs that relax smooth muscle. (James at p. 245, col. 3.) According to James, bronchodilation does not need to be limited to reversal of excessive smooth muscle contraction, but rather reversing the muscle contraction can also be applied for non-excessive muscle contraction of thickened airway walls to increase airway caliber and lower the resistance to a similar degree. (James at p. 245, col. 3.) Based on these findings, James concludes that changes produced by chronic inflammatory processes can lead to excessive airway narrowing without excessive smooth muscle contraction

such that the treatment of asthma should focus on (a) reversing the inflammatory changes in the airway wall and (b) relaxation of the airway smooth muscle. (James at p. 246, col. 1.)

8. Before the present invention, there were several teachings in the prior art that airway smooth muscle was of the utmost importance and was indispensable for respiration. (Macklin, C.C., *The Musculature of the Bronchi and Lungs*, Physiol. Rev. (1929) 9:1-60.) As set forth in Mitzner, W., *Airway Smooth Muscle The Appendix of the Lung*, American Journal of Critical Care Medicine, (2004) 169:787-790 ("Mitzner"), the early body of literature dating back over a 125 year period taught that airway smooth muscle had one or more functional purposes. Although Mitzner cites later articles as refuting some of the functional purposes of airway smooth muscle, Mitzner also points out that other listed functional purposes were still thought to be valid as late as 2004 (e.g., peristalsis to assist exhalation). Therefore, in 1998, a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose and that airway smooth muscle cells should not be killed.

9. In 1998, the United States Food and Drug Administration also held the prevailing view of the time that airway smooth muscle was important for normal lung function. This was one reason why the United States Food and Drug Administration (USFDA) did not grant Asthmatx, Inc. approval to treat asthma in a human patient by debulking airway smooth muscle tissue until 2005. For example, in response to an Investigational Device Exemption application regarding Asthmatx's Alair System, the USFDA stated:

> Airway smooth muscle facilitates airway dilation as well as airway constriction. Of concern is that ablation of airway smooth muscle in small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway bronchospasm and then be unable to effectively cough

and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways, coupled with underlying asthma, could lead to complications such as bronchiectasis.

(USFDA Letter dated 16 February 2001 regarding IDE No. G010016 attached in redacted format.)

10. James does not teach or otherwise suggest debulking or reducing the mass of the airway smooth muscle to reverse inflammatory changes for treating asthma. First, James teaches that the increase in airway wall thickness associated with asthma is not confined to the airway smooth muscle, but rather inflammation of the submucosa and the epithelium also contribute to the increased airway wall thickness. Second, James does not teach any mechanism to reverse the inflammation of the airway wall. Third, as explained in Paragraph 8 above, a person of ordinary skill in the art in 1998 would have understood that destruction or removal of airway smooth muscle was controversial because the prevailing view at that time was that airway smooth muscle performed a functional purpose essential to normal lung function. Therefore, in 1998, a person skilled in the art would not understand James to mean that asthma should, or even could, be treated by debulking the airway smooth muscle.

11. James expressly teaches that the treatment of asthma should focus on reversing the inflammatory changes in the airway wall and relaxation of the airway smooth muscle. A person of ordinary skill in the art would understand that reversing inflammatory changes in the airway involves acute reversal of inflammation of the submucosa and epithelium as opposed to debulking the airway smooth muscle because (a) the prevailing view in 1998 was that airway smooth muscle had a functional purpose and therefore should not be killed, (b) debulking does not provide acute relief, and (c) pharmaceutical treatment of the epithelium may provide acute relief.

12. Regunathan discloses that vascular hyperplasia, i.e., the excessive proliferation and hypertrophy of vascular smooth muscle cells, is a major pathogenic mechanism contributing to vascular pathology in atherosclerosis, hypertension resulting from renal artery stenosis and other causes, restenosis of coronary and other arteries after coronary angioplasty, insertion of vascular stents, and other conditions. (Regunathan at 1:17-27.) The invention of Regunathan is directed to a non-invasive method of inhibiting the initiation or progression of vascular hyperplasia and, in particular, to inhibiting proliferation of vascular smooth muscle cells. (Regunathan at 1:34-37.) Regunathan, more specifically, teaches a method of inhibiting the proliferation of vascular smooth muscle cells by administering a vascular smooth muscle cell anti-proliferative effective amount of an I_2 imidazoline receptor agonist. (Regunathan at 1:37-42.)

13. Clarke is directed toward inhibiting restenosis associated with angioplasty and teaches that intimal hyperplasia or proliferation of vascular smooth muscle cells is a major factor in restenosis. (Clarke at 1:1-5 and 1:41-43.) Clarke further teaches vascular smooth muscle cells enter their growth cycle 2-3 days after injury and the majority of the vascular smooth muscle cells cease to proliferate within 7 days after injury. (Clarke at 1:43-50.) Clarke indicates that the total number of smooth muscle cells reaches a peak about two weeks after injury and remains constant for up to one year; Clarke states this suggests that a reduction of the number of smooth muscle cells injured during angioplasty will reduce the likelihood of subsequent restenosis. (Clarke at 1:50-55.) To inhibit restenosis, Clarke teaches reducing the proliferation of additional vascular smooth muscle cells in the blood vessel walls at an angioplasty site by irradiating the angioplasty site with the appropriate radiation in the UV wavelength range. (Clarke at 2:39-44.) The irradiation kills a major portion of the injured smooth muscle cells in the media so that few, if any, smooth muscle cells remain in the angioplasty site to proliferate and cause restenosis. (Clarke

at 5:1-9.) However, as shown in Figures 3B and 3C, the thickness of media is not reduced by the process.

14. In 1998, as well as now, a person of ordinary skill in the art would have understood that the purpose of both Regunathan and Clarke was to inhibit injured vascular smooth muscle cells from producing additional vascular smooth muscle cells that would normally occur in response to damage, injury or other trauma to the vessel wall. With respect to vascular structures, restenosis is caused by hyperplasia as opposed to hypertrophy of smooth muscle cells. Hyperplasia in vascular applications is the excessive proliferation of new or additional cells above the level of normal cell production, whereas hypertrophy is the increase in tissue size caused by the filling with connective and scar tissue without necessarily increasing the number of smooth muscle cells above normal levels. A person of ordinary skill in the art would accordingly understand that Regunathan and Clarke are limited to methods for reducing or inhibiting injured vascular smooth cells from producing additional smooth muscle cells to prevent hyperplasia.

15. Additionally, to a person of ordinary skill in the art, neither Regunathan nor Clarke teaches debulking or otherwise removing uninjured vascular smooth muscle tissue that existed before the injury occurred. First, Regunathan and Clarke are both clear that hyperplasia (i.e., an increase in the number of cells) as opposed to hypertrophy (i.e., an increase in tissue size caused by the filling with connective and scar tissue) causes restenosis. Second, both Regunathan and Clarke teach methods for inhibiting the production of additional smooth muscle cells, but neither reference discloses debulking uninjured smooth muscle tissue that existed before injuring the vessel. Third, vascular smooth muscle provides an essential function for maintaining blood pressure through vasoconstriction and vasodilation, and as such a person skilled in the art would not apply the methods taught in Regunathan and/or Clarke in a manner that would

debulk the existing vascular smooth muscle tissue. Therefore, without an injury or other condition that causes proliferation of the smooth muscle tissue, a person of ordinary skill in the art would not apply the methods taught by Clarke and/or Regunathan to airway smooth muscle or any other smooth muscle tissue in the body.

16. On 10 June 1998, I filed the present application directed to a radical method for treating asthma by irradiating the walls of an airway of an asthmatic lung with a source of energy at a wavelength and intensity that, over time, causes debulking of airway smooth muscle tissue and prevents the lung tissue from replicating. The airway smooth muscle tissue is irradiated such that the ability of the airway to contract is reduced.

17. In an asthmatic lung, the increase in thickness of the airway smooth muscle is caused by hypertrophy - not hyperplasia. As such, the airway smooth muscle does not suffer from an abnormally high proliferation of additional cells, but rather it is the increase in size of the uninjured airway tissue that contributes to the increase in airway wall thickness. By debulking the airway smooth muscle as set forth in several embodiments of my invention, the mass of the airway smooth muscle is reduced so as to reduce the ability of the airway to contract. This directly contradicts the position that Clarke's method would be applied to an asthmatic lung in accordance with the claimed method to decrease hypertrophy.

18. A person of ordinary skill in the art would not irradiate an uninjured airway wall of an asthmatic lung at a wavelength and intensity that, over time, would debulk airway smooth muscle based on the teachings of James, Regunathan or Clarke, either individually or collectively. Clarke teaches applying the UV radiation in a manner that kills a portion of the injured smooth muscle cells to prevent or inhibit additional smooth muscle cells from proliferating. Clarke, in effect, proactively kills injured smooth muscle cells before their growth cycle to prevent the proliferation of additional

cells. However, as explained above in Paragraph 15, without an injury or other condition that causes proliferation of smooth muscle cells, there is no reason to apply Clarke's method to airway smooth muscle or any other smooth muscle. Clarke accordingly does not teach debulking the smooth muscle cells, and a person of ordinary skill in the art would not apply Clarke in a manner that would cause such debulking because, at least in part, vascular smooth muscle provides an essential function for maintaining blood pressure. Regunathan similarly teaches inhibiting proliferation of smooth muscle cells as opposed to debulking the smooth muscle tissue. Lastly, James does not teach debulking the airway smooth muscle, and a person of ordinary skill in the art in 1998 would not understand James to mean that asthma should, or even could, be treated by debulking the airway smooth muscle. Unlike the cited references that are directed to preventing the proliferation of smooth muscle cells, several embodiments of my treatment seek to debulk existing uninjured airway smooth muscle affected by hypertrophy to provide a cure for chronic conditions. Therefore, it would not have been obvious to a person of ordinary skill in the art at the time of the invention to use the method of Clarke to treat asthma in light of the teachings of Regunathan and James.

19. Additionally, even if Clarke's method was applied to an asthmatic airway, it would not result in debulking of the airway smooth muscle tissue. Vascular structures and airway structures are significantly different such that Clarke's method would be ineffective for debulking airway smooth muscle. Unlike the smooth lining of the endothelium in blood vessels, the epithelium in asthmatic airways has several folds (see, e.g., Figure 1 of filed application). Clarke teaches applying the UV radiation at a relatively low angle to the lumen wall that would result in shadowing within the airway such that some of the airway smooth muscle would not be treated, or at least not sufficiently treated, for debulking. The airway epithelium, which is comprised of tight junctions of columnar cells, is 10-15 times thicker than the single flat layer of squamous cells that comprise the

vascular endothelium. Further, the airway epithelium necessarily facilitates diffusion of nitrogen for proper lung function while the endothelium prevents nitrogen diffusion and nitrogen-containing substances, and nitrogen monoxide in particular, which has a direct affect on causing vascular smooth muscle to contract, which could be catastrophic in an airway. The airway epithelium and blood vessel endothelium are accordingly two different materials with different properties that react differently to irradiation. As a result, a person of ordinary skill in the art would understand that the intensity level of Clarke's UV radiation to treat restenosis in a blood vessel would not likely be sufficient to debulk airway smooth muscle through the epithelium of an airway.

20. Ivanyuta is directed to treating chronic non-obstructive bronchitis. Ivanyuta discloses that disruptions of local and systemic immunity are involved in chronic non-obstructive bronchitis. (Ivanyuta at 1.) Ivanyuta teaches that the efficacy of drugs may not satisfy clinical physicians and that lasers have been proven to affect the pathologic process and immunocompetent cells. (Ivanyuta at 1.) Ivanyuta studied the efficacy of endobronchial low-power laser therapy and its effect on the immune status of patients with chronic non-obstructive bronchitis. (Ivanyuta at 2.) More specifically, Ivanyuta irradiated the mucosa of the trachea and bronchi during fibrobronchoscopy using red light at a wavelength of 633 nm and a power of 6-8 mW at the light-guide exit. (Ivanyuta at 2.) The total dose applied during a session ranged from 2.1-3 J, and sessions were conducted every other day for a course of four to seven procedures. (Ivanyuta at 2.) Ivanyuta teaches that the patients exhibited the characteristic dynamics of bronchial lesions. (Ivanyuta at 3.) Ivanyuta states that some aggravation occurred after one or two procedures resulting in an initial intensification of coughing and increase of sputum; after an undisclosed time period, the coughing stopped or decreased

significantly and the sense of tickling of the throat went away. (Ivanyuta at 3.)

21. A person of ordinary skill in the art would not irradiate an airway wall of an asthmatic lung to treat asthma based on Ivanyuta. First, Ivanyuta is directed to treating chronic non-obstructive bronchitis such that this reference is not directed to asthma or another obstructive pulmonary disease. Second, Ivanyuta fails to provide any teaching regarding asthma and does not discuss either hypertrophy or hyperplasia. Third, as noted above in Paragraphs 8 and 9, a person of ordinary skill in the art and the USFDA understood that airway smooth muscle was important for normal lung function at the time of the present invention. Therefore, Ivanyuta would not lead a person of ordinary skill in the art to irradiate an airway wall of an asthmatic lung to treat asthma.

22. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

7/2/2008
Date

Michael D. Lauer, M.D.

Attachment 1a

USFDA Letter dated 16 February 2001, regarding IDE No. G010016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 16 2001

Mr. Timothy R. Williams
Director of Regulatory and Clinical Affairs
Broncus Technologies, Inc.
1400 N. Shoreline Boulevard Bldg. A, Suite 8
Mountain View, CA 94043

Re: IDE Number G010016
Alair System
Dated: January 17, 2001
Received: January 18, 2001

Dear Mr. Williams:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. We regret to inform you that your application is disapproved and you may not begin your investigation. Please be advised that, based on the data that you have provided, we believe that studies in humans pose significant potential risks that appear to outweigh the potential benefits. Our disapproval is based on the following deficiencies:

1. You provided pre-clinical data using the canine model. In total, there were nine animal studies performed to support this IDE application, with a total of 37 canines treated and over 2300 device activations.

   You have also provided the results of data collected outside of the United States (OUS) trial where one lobe was treated in 8 patients, 1 to 3 weeks before a scheduled lobectomy. There were 3 to 9 activations in each patient, for a total of 41 activations.

Even if normal healing of the larger treated bronchi were to occur, there are significant concerns that the underlying condition (asthma) would nonetheless remain. Airway smooth muscle facilitates airway dilation as well as airway constriction. Of concern is that ablation of airway smooth muscle in small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway bronchospasm and then be unable to effectively cough and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways, coupled with underlying asthma, could lead to complications such as bronchiectasis.

If you submit information correcting the deficiencies, we will reevaluate your application. The information should be identified as an IDE amendment referencing the IDE number above, and must be submitted in triplicate to:

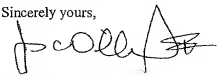
IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Alternatively, you may request a regulatory hearing regarding the disapproval of your IDE application. The enclosure "Procedures to Request a Regulatory Hearing" describes how to submit such a request. The procedures governing a regulatory hearing are described in the regulations at 21 CFR Part 16.

If you prefer not to request a regulatory hearing, you may nevertheless request that this decision be reviewed by the IDE Review Committee within the Office of Device Evaluation (ODE). The enclosure entitled, "IDE Review Committee and Procedures to Request Review" discusses the purpose and operation of the Committee as well as how to submit such a request to the Committee.

If you have any questions, please contact Frank Lacy at (301) 443-8517 ext-170.

Sincerely yours,



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Enclosures
(1) Procedures to Request a Regulatory Hearing
(2) IDE Review Committee and Procedures to Request Review

APPENDIX C

In the related proceedings referenced in II. above, no answers from the Examiner or decisions from the Board of Patent Appeals and Interference have been filed. As such, copies of decisions in related proceedings are not provided.